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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,156	02/28/2002	John N. Feder	D0115 NP	2664

23914 7590 08/12/2003

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	11

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,156	FEDER ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) *33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-32 and 34-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 21 May 2003 (Paper No. 10) has been entered. Claims 1-20 are canceled. Claim 33 is withdrawn by the examiner. Claim 21 is amended. Claims 21-32 and 34-40 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office action.

Withdrawn Objections and/or Rejections

Sequence Rules

The objection to the specification because the Figures did not properly recite SEQ ID NO's as set forth at p. 3 of the previous Office Action (Paper No. 9, 10 February 2003) is *withdrawn* in view of the explanation by the Applicant (Paper No. 10, 21 May 2003) that the SEQ ID NOs for each sequence in the figures can be found in the Brief Description section of the instant Specification.

URL's

The objection to the specification because it contained browser-executable code as set forth at p. 3 of the previous Office Action (Paper No. 9, 10 February 2003) is *withdrawn* in view of the amendment which removed all hypertext links from the disclosure (Paper No. 10, 21 May 2003).

35 USC § 112, second paragraph

The rejection of Claim 21 as being indefinite, as set forth at p. 11-12 of the previous Office Action (Paper No. 9, 10 February 2003) is *withdrawn in part* in view of the amendment which added definite language ("comprising") and removed a broad term ("antisense") that was used to define a broader term ("complimentary sequence") (Paper No. 10, 21 May 2003).

35 USC § 112, first paragraph - Written Description

The rejection of Claims 37-40 for lack of Written Description as set forth at p. 12-14 of the previous Office Action (Paper No. 9, 10 February 2003) is *withdrawn* in view of the arguments put forth by the Applicant (Paper No. 10, 21 May 2003, pages 20-21).

Maintained Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 21-32 and 34-40 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-10 of the previous Office Action (Paper No. 9, 10 February 2003). Claims 21-32 and 34-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (Paper No. 9, 10 February 2003), one skilled in the art clearly would not know how to use the claimed invention.

The claims are directed to a nucleotide that encodes a protein that possesses approximately 51-55% homology to previously-identified polypeptides, such as: *sequence 29*

(1996, Kim, et al, Accession No. AAB15537) and a protein product from mice (2002, Carninci, et al, Accession No. BAC38959). As discussed in the previous Office Action (p. 5), no well-established utility exists for newly isolated complex biological molecules. The specification does not disclose experiments that impart *any* function for the polypeptide encoded by the claimed nucleotide in the context of the cell or organism. The specification does not teach the skilled artisan how to use the disclosed *K+betaM5* peptide for any unique or specific purpose. For example, there is no disclosure of the use of inhibitors for the channel, or of ion-channel specific characteristics such as its Nernst potential or conductance, or of changes in conductivity based on ion-concentration experiments, or of patch-clamp experiments, or of physiological changes in transfected cells, or of the phenotypes of "knock-in" or "knock-out" organisms, or of diseases caused by an overactivity or underactivity of the channel. The skilled artisan is not provided with sufficient guidance to use the claimed polynucleotides for any purpose unique to *this* channel.

Applicants contend (page 8) that the courts have defined Utility requirements more broadly than those applied in examination of the current Application, stating "[A] 'rigorous correlation need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient" and cites *Fujikawa v Wattanasin* (1996, 39 USPQ2d 1895 1900). However, the fact patterns of the case cited by the Applicant are significantly different than those discussed in the current Office Action. The cited court decision is therefore not significant or binding with regard to the instant rejections. *Fujikawa v Wattanasin* centered on species of novel mevalonolactones, chemical compounds with structures somewhat like steroids. The claimed invention was a method of inhibiting the biosynthesis of cholesterol by administering to patients an appropriate

dose of a compound falling within the scope of the genus of mevalonolactones. Well-described species of a genus of *chemical structures* may well have utility based upon their homology to other members of a class. For novel polypeptides, however, this is seldom the case. As the Utility Guidelines (Federal Register, 2001, 66: 1092-1099) go on to say after the discussion of *Fujikawa v Wattanasin,* "where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class. When there is a reason to doubt the functional protein assignment, the utility examination may turn to whether or not the asserted protein encoded by a claimed nucleic acid has a well- established use. If there is a well-established utility for the protein and the claimed nucleic acid, the claim would meet the requirements for utility under 35 U.S.C. 101. If not, the burden shifts to the applicant to provide evidence supporting a well-established utility. *There is no per se rule regarding homology, and each application must be judged on its own merits."* (italics added).

Applicants then discuss the various diseases that may be treated by ligands of the disclosed polypeptide (p 8-9). These include "epilepsy, Bartter's syndrome, persistent hyperinsulinemic hypoglycemia of infancy, hyperkalemia and hypokalemia, cystic fibrosis and hypercalciuric nephrolithiosis," all diseases with underlying etiologies that are unique and specific for each, and surely do not involve perturbations in the *K+betaM5* peptide disclosed in the instant Application. Cystic fibrosis is a good example of a well-characterized disease related to a mutation in a specific ion channel (the CFTR-chloride channel). Similar *specific*

identification of a disease state with the *K+betaM5* channel is one of many lines of evidence that could impart a function to the claimed polynucleotide.

Applicants further discuss the use of antibodies and immunohistochemistry to impart a function to the claimed polynucleotide encoding *K+betaM5*, stating on page 10:

"tissue profiling was performed that localized expression of the claimed polypeptides to testis, spinal cord, lymph node, heart, uterus, and to a lesser extent, in small intestine stomach, prostate, and kidney (see Figure 8)."

Contrary to the Applicant's contentions that these data provide "specific and substantial details of the claimed polynucleotides", it is difficult to associate *specificity* with a polypeptide that occurs in a multitude of normal and unrelated tissues. Nor is there a substantial function that can be associated with a polypeptide that is not associated -by tissue staining or otherwise- with a change in tissue function or with a disease state.

Applicants then discuss the utility of antibodies made against the *K+betaM5 polypeptide*. As discussed in the previous Office Action (Paper No. 9, 10 February 2003), the usefulness of antibodies rests on the utility of the protein against which they are made. This is because antibodies are made by unknown and random recombinations of a B-cell's genome, which may yield a large number of possible antibodies that bind the same peptide, and also because it is not known and not predictable what the exact epitope/antibody binding configuration is. An applicant may therefore patent all antibodies that bind to a particular polypeptide or epitope, provided it itself has a function (see, for example Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, Docket 87-1454, and the Federal Register, 2001, p 1097, 3rd column).

The Applicant argues that since "the polypeptides and polynucleotides of the present invention have been specifically and substantially described in the specification", that this "knowledge can be employed to make, study and use *variants* of the claimed polypeptides and polynucleotides" (Paper 10, 21 may, 2003, page 10), italics added by examiner.

However, there is a lack of guidance in the Specification and prior art as to what structure is required for the protein variants encompassed by Claims 37-40. Applicant's arguments that one could merely test for activity is not sufficient for an enabling disclosure. Additionally, the Specification fails to teach *which* activity is possessed by the disclosed full-length non-variant polypeptide encoded by the *K+betaM5* polynucleotide. The breadth of these claims is still extensive. Applicants have not provided any guidance or working examples regarding mutations that have been made to the polynucleotide encoding *K+betaM5* and the resultant activity of the channel. Furthermore, it is not predictable, based on peptide sequence, what that activity might be. For example, there is no discussion of specific ligands for all or many variant channels, or the physiology of knock-out animals, or transduction processes in cells transfected with the variants, to name a few examples.

Applicants then discuss "Binding Assays", stating that "knowledge of the precise nature of the binding site(s) of the claimed invention is not required to practice screening methods involving the claimed polypeptide", and point to examples of the methodology of assays described in the Specification (such as on page 210).

As discussed in the previous Office Action (Paper 9) the discussion of binding sites in the instant Specification is not enabling for the disclosed channel protein because it is not

substantial. The specification does not characterize the polypeptide encoded by the polynucleotide of the claimed invention. Therefore binding sites, ligands, etc. are not identified. However, the identification of binding sites on the *K+betaM5* polypeptide is one example, out of many possible, of a substantial piece of evidence that would impart a function on the disclosed polypeptide. The examiner agrees that it, by itself, is not necessary, provided other evidence of function is presented.

Applicants take issue with the previous discussion (Paper 9, pages 6 and 7) in which tissue expression of the *K+betaM5* polypeptide was characterized as not *substantial.* Applicants demonstrated that the *K+betaM5* polypeptide is expressed in a wide variety of normal tissues, including the testis, liver, small intestine, spinal cord, breast, etc. Applicants state that this is a "real world" context of use (Paper 9, page 12), and further discuss the *Drosophila* ortholog as involved in the NF-κB pathway.

As discussed in the previous Office Action, patentable utility of tissue typing for the polynucleotide encoding the claimed polypeptide is not substantial because one skilled in the art would not readily use the nucleotide sequences for tissue-typing in a real world sense as the protein is not specific to one tissue and is not associated with any disease or disorder. Evidence of mere expression in a tissue is not tantamount to a showing of a role for the polynucleotide of the present invention. It is not clear if expression of the polynucleotide of the present Invention is correlated with a specific change in physiology, for example, or with a disease state. Furthermore, the supposed association with the NF-κB pathway is not substantial, even if confirmed, because the pathway is a general one upon which many transduction pathways converge.

Applicants then discuss *Brana* (1995, 51 F.3d 1560, 34 U.S.P.Q.2d 1436) in terms of the credibility of the proposed utility of the disclosed channel polypeptide, stating that the Brana ruling "indicated that unless the invention involves an inherently unbelievable undertaking or involves implausible scientific principles, or is contravened by evidence proffered by the Patent office, an asserted utility must be accepted."

However, the main ruling in *Brana* was that

"FDA approval . . . is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans."

The previous Office Action makes no mention of FDA approval, nor of the *credibility* of the assertions of function associated with the *K+betaM5* polypeptide, nor indicated that the invention involves an inherently unbelievable undertaking or involves implausible scientific principles. The Applicant is asked to clarify what is meant by this discussion (Paper 10, 21 May 2003, pages 12-13).

Applicants argue that the Patent Office has "adopted an inappropriate standard for measuring enablement" (page 14, 21 May 2003, Paper No. 9) and discusses the significance of this in pages 14-19. Applicants submit that the nucleotide of the instant Specification encodes a potassium channel, important in the etiology of several neurological and immunological disorders. Applicants imply and discuss that homology of the disclosed polypeptide with a class

of proteins *already having* utility shall impart sufficient utility on the novel polypeptide and on the polynucleotide encoding it. However, the polypeptide of the Instant Specification and the polynucleotide encoding are, as yet, unidentified molecules. They possess only moderate (51-55%) homology to known gene products (above), which are themselves uncharacterized. Very little additional information is given in the Specification about a unique or specific function for the claimed polynucleotide(s).

However, specific functional, physiological or pharmacological data is precisely the type of evidence that would serve to enable the instant invention. Despite the Applicant's arguments (Paper No. 9, 21 May 2003) the Patent Office makes clear that the usefulness of new polynucleotides does not include "entry point" and speculative experiments (Federal Register, 2001, 66: 1094). There is no evidence that the protein disclosed in the instant Specification functions as potassium channel. However, even if it were established as such, additional specific functional assays would be needed since this family of proteins is very large and enormously varied (as discussed in the previous Office Action, page 9). Therefore, one skilled in the art would not know the utility and function of the polypeptide disclosed in the instant disclosure, even if it *were* a potassium channel because, as discussed in the related art above and the specification of the instant application: "Voltage-gated potassium channels are a large and diverse family of proteins" (p. 1 of Specification).

35 USC § 112, second paragraph

The rejection of Claim 21 as being indefinite as set forth at p. 11-12 of the previous Office Action (Paper No. 9, 10 February 2003) is *maintained in part.* Claim 21 contains a

reference to "stringent" hybridization language without defining the term in the claim. Applicants refer to the definition of "stringent" in the Specification on page 74 (page 23, Paper No. 10, 21 May 2003; however the independent claim itself must define use of the word "stringent".

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW
8/6/03

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